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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,313	11/28/2000	Elmar Reinhold Burchardt	LeA 32 701	8752

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/701,313	BURCHARDT ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/31/07, is acknowledged.

2. Claims 1-2 and 6-10 are pending and under examination in the instant application as they read on a monoclonal antibody directed against an epitope within the 30 most N-terminal amino acids of human PIIINP, or an oligopeptide with the sequence derived from the N-terminal peptide is of Co12 domain of PIIINP, and the 30 most N-terminal amino acids of human PIIINP as the species

3. Applicant's IDS, filed 8/31/07, is acknowledged.

4. The oath or declaration stands defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the Post Office Address and Residence of inventor Elmar Reinhold Burchardt is altered without been initialed and dated. Any changes made in ink in the application or oath prior to signing should be initialed and dated by applicants prior to execution of the oath or declaration. The Office will not consider whether non-initialed and/or non-dated alterations were made before or after signing of the oath or declaration. See MPEP 605.04(a).

Applicants indicate that they will provide the Office with a new declaration in short order, the objection is maintained until such declaration is provided.

5. Claims 1 and 8 are objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims.

6. Claim 8 is objected to because the claim contains two periods (..) at the end of the claim.

7. In view of the amendment filed on 8/31/07, only the following rejections are remained.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The recitation "characterized by preferential binding" in Claim 2 is indefinite because the narrow range binding within the broad range binding using the term "preferentially"

renders the claim indefinite. The metes and bounds of such preferential binding are ambiguous and unclear and, in turn, the metes and bounds of the claimed "monoclonal antibody" are not defined.

Applicant did not address this rejection. The rejection is maintained for reasons of record.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-2 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brocks et al , 1993, (IDS ref.) in view of U.S. Pat. No. 5,512,283, as is evidenced by GenBank accession No. P02461 for the same reasons set forth in the previous Office Action mailed 6/4/07.

Applicant's arguments, filed 8/31/07, have been fully considered, but have not been found convincing.

Applicant submits that it has historically been exceedingly difficult to provide antibodies against collagen molecules, particularly collagen III, that specifically recognize the human protein. This is apparent from the extensive description of the prior art that shows that numerous investigators had, for several decades, tried to provide such molecules. These were directed against various portions of the molecule. However, until the present invention, it was not clear that an antibody that could recognize the 30 most N-terminal amino acids of the PIIINP would be useful for such specific recognition, and would be able to differentiate between collagen breakdown and collagen synthesis. An antibody described in the present specification and recited in the amended claims is now used in a commercially available Enhanced Liver Fibrosis test, the first CE-marked, standardized non-invasive blood test for assessing the status of liver fibrosis in a patient.

In contrast to applicant's assertion, no objective evidence has been provided to indicate that the art known process of generating antibodies, including generating monoclonal antibodies for over the past 25 years, to antigens/polypeptides of interest would not be successful given the prior art teaching.

Applicants note that Brocks describes the production of polyclonal antibodies against a - synthetic peptide representing the 14 C-terminal amino acids of the N-terminal propeptide of rat and bovine procollagen type III. The goal in Brocks was to identify antibodies that did not react with the Coll domain. As noted in Brocks, "this antigenic domain is not present in the Coil antigen" (page 382, left column, second paragraph). There is no teaching or suggestion in Brocks that an antigen of interest would be the 30-most N-terminal amino acids of the human protein.

Contrary to applicant assertions Broke uses 128 pins carrying peptides of 8 amino acids were synthesized from the bovine N-terminal propeptide of procollagen type III. The first pin carried a peptide representing amino acids 13-26, the last pin represented amino acids 146-153 (see [age 383 under *Epitope scanning* in particular). Actually, Fig. 1 legend teaching that that 128 pins carring peptides of 8 amino acids were synthesized, covering the entire length of the N-terminal propeptide with the exception of the signal peptide. The amino acid number refers to the ssequence of the entire N-terminal propeptide, beginning at the translation start site. The peptides used for epitope scanning are represented on the X-axis by their N-terminal amino acid. Accordingly, Broke et al teach the following peptides:

Bovine ^{19}TIILAQQE^{26}
Human ^{19}TIILAQQE^{26}

Bovine ^{20}IILAQQEA^{27}
Human ^{20}IILAQQEA^{27}

Bovine ^{21}ILAQQEAV^{28}
Human ^{21}ILAQQEAV^{28}

Bovine ^{22}LAQQEAVE^{29}
Human ^{22}LAQQEAVE^{29}

Bovine ^{23}AQQEAVEG^{30}
Human ^{23}AQQEAVEG^{30}

Given the high sequence identity between the referenced/claimed peptides; the resultant antibodies would have the expected property of binding human "30 most N-terminal amino acids of PIIINP" in the absence of objective evidence to the contrary.

Applicant contends that the presently claimed antibodies specifically recognize the 30 most N-terminal amino acids of the human protein. The disclosure of antibody generation in Brocks is directed at both an entirely different species and an entirely different molecular entity. Even if one of skill in the art would have chosen to produce monoclonal antibodies based on the peptide sequence in Brocks, it would have been a different antibody.

Contrary to applicant assertions, given the high sequence identity (i.e., 100%) between the referenced/claimed sequence; the resultant antibodies would have the expected property of

binding human "30 most N-terminal amino acids of PIIINP" in the absence of objective evidence to the contrary.

Furthermore, as noted in Brocks, human antigen was non-reactive against the antibody generated (see abst.). One of skill in the art would not have been motivated to make any further antibodies based on the disclosure in Brooks for the purpose of using it against human antigens.

However, the "non-reactive" statement in Brocks' abstract is referring to the N-terminal propeptide of procollagen type III (full length) not to the specific peptide, above. (see table III, on page 385).

Applicant concludes that there would be no motivation to use any peptide sequences disclosed in Brooks to produce a monoclonal antibody by the methods described in the '283 patent. Furthermore, as the antibody of Brooks did not recognize the human protein, there is no reason that one of skill in the art would expect any antibody produced using this sequence to specifically recognize the 30-most N-terminal amino acids of the human Col1 domain, as recited in the amended claims. Therefore, the references cited, alone or in combination, do not suggest the production of an antibody directed against the 30 most N-terminal amino acids of the Col I region, as recited in the amended claims.

However, given the high sequence identity between the referenced/claimed "30 most N-terminal amino acids" of human PIIINP; the referenced antibodies would have the expected property of binding human 30 most N-terminal amino acids of PIIINP in the absence of objective evidence to the contrary. In addition, applicant is invited to consider the following decisions based upon generating antibodies to proteins of interest. Whether the rejection is based on "inherence" under 35 U.S.C. § 102 or prima facie obviousness under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. Examiner properly shifted burden to applicant to establish, through objective evidence, that hybridoma and monoclonal antibody of invention differ in unobvious manner from those of the prior art references. Ex parte Phillips, 28 USPQ2d 1302 (BPAI 1993). It is our finding that once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies. Ex parte Erlich, 3 USPQ2d 1011, 1015 (BPAI 1986).

12. The following new ground of rejections are necessitated by the amendment and IDS submitted 8/31/07.

13. Claims 6-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 6-7 and 9 are indefinite in the recitation of "35J22" and "35J23" because its characteristics are not known. The use of "35J22" and "35J23" monoclonal antibodies as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because "35J22" and "35J23" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct hybridomas or cell lines. It is suggested that the deposit accession No. be cited in the claims.

B) The recitation "wherein said/the monoclonal antibody" recited in claims 8-9 is ambiguous. Claim 8 recites two monoclonal antibodies (first and second) it is not clear which antibody the said monoclonal antibody refers to, the first or the second mAb.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "a sandwish immunoassay product comprising" claimed in claim 8-10, and "a monoclonal antibody bound to a support" recited in claims 8-9 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 8/31/07 dose not points to the specification for support for the newly added limitations "sandwish immunoassay product comprising" as claimed in claims 8-10 and "a monoclonal antibody bound to a support" as claimed in claim 8. However, the specification does not provide a clear support for such limitation. It is noted that original claim 5, and the specification (page 12, lines 7-11, page 23, lines 27-30) use the term immunoassay as a verb (i.e., method) not as a noun (i.e., product). The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

15. Claims 6-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma that produce 35J22 and 35J23 mAb antibodies are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposits were made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

16. Claims 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brocks et al , 1993, (IDS ref.) in view of U.S. Pat. No. 5,512,283, as is evidenced by GenBank accession No. P02461 and US. Patent No. 5,434,088.

The teachings of Brocks and the '283 patent have been discussed, supra.

The claimed invention differs from the reference teachings only in the recitation of a sandwich immunoassay production comprising first and second mAb comprising a detectable label in claims 8 and 10.

The `088 patent teaches that a target substance is detected by a sandwich immunoassay using fine particle (A) having bound to it a fluorescer and an antibody reacting specifically with the target substance, and a fine particle (B) having bound to it a quencher and an antibody reacting specifically with the target substance, through a different antigenic determinant. Also disclosed is a competitive immunoassay having a fine particle (C) bound to it a fluorescer or a quencher, and an antibody reacting specifically with the target substance, a bound product (D) composed of the remainder of the fluorescer and the quencher, or a known amount of the target substance. Binding of the fluorescer and the quencher to the fine particle (A), (B) or (C) is affected so that the fluorescer and the quencher are covalently bound to a substance adsorbed on the fine particle. The sandwich immunoassay is advantageously conducted using a kit containing (i) the fluorescer- and antibody-bound fine particle (A) and (ii) the quencher- and antibody-bound fine particle (B). The competitive immunoassay is advantageously conducted by using a kit containing (i) the fluorescer- or quencher-and-the antibody-bound fine particle (C), and (ii) the bound product (D) of the quencher or fluorescer and the target substance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the resultant antibodies in a sandwich immunoassay kit. Given that at least two antibodies to different N-terminal peptides of PIIINP would result from the teachings of Brocks et al in view of `283, one antibody would bound to a support and the second mAb would be labeled.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the competitive immunoassay is advantageously conducted by using a kit as taught by the `088 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 18, 2007

Maher Haddad

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